REMARKS

This is in response to the office action mailed September 22, 2003. A Petition for a one month extension of time with fee is enclosed herewith.

Claims 1 to 26 are pending in this application. Claims 20 to 25 are withdrawn from consideration.

Claims 1 to 19 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Appropriate amendments to claims 1, 14 and 15, without prejudice, have been made to avoid this rejection. However, Applicant submits that the "v/v" unit would be clearly known to a person skilled in the art and those reading the specification would understand this measure.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, and to the extent that this rejection is understood, an amendment has been introduced to address the Examiner's comments.

Claims 1, 5 to 11, 13 to 19 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen in view of Bignami. Hansen is cited as showing aspects of the claimed invention (as set out in paragraph 5 of the office action), while Bignami is cited as teaching the adding of surfactants.

The claimed invention

Once more, it is apposite to point out the claimed specific steps of the method of the invention, the order of the steps and the effect of each step in formulating the no wash bead assay. (Of course, the order is relevant insofar as a previous step is required for a subsequent step and not necessarily to the

preparation of the starting materials For example, it does not matter if the first reagent is prepared before the second reagent, since the once does not require the other to carry out the invention.)

The Examiner is requested to bear in mind that the claimed invention is not a random arrangement of general components, but is a combination of specifically directed components in a particular order. This fact must not be lost sight of, since it produces an assay having properties and characteristics which are vastly different from that of the cited references.

Claim 1 thus requires the following for the *method of making a no wash bead based assay*:

(1) A first reagent comprising a *buffer* is prepared.

(2) A second reagent comprising a *protein* is prepared.

(3) *Beads* of preselected size and having a coefficient of variation less than 5% are prepared. This preparation step includes washing the beads in the buffer to form a *bead-buffer matrix* and *reducing the surfactancy* of the beads to no more than 5% to allow antigens to attach to the beads

(4) An *antigen* for detecting the presence of a target species is added to the bead-buffer matrix such that the antigen attaches to the beads to form a *bead-antigen mixture*, the surfactancy of the beads facilitating attachment of the antigen thereto.

(5) The first reagent buffer is added to the bead-antigen mixture and the *mixture* is thereafter incubated.

(6) The second reagent is added to the bead-antigen mixture to *reduce or eliminate non-specific binding sites*.

Neither Hansen, Bignami nor Fulwyler, individually or in

combination, discloses such a specific set of steps with the components recited. In the office action, the Examiner parcels together disparate and, it is submitted, unrelated bits and pieces from Hansen, but even the very points made by the Examiner fail to add up to the invention as claimed. The Examiner is requested to not lose sight of the *claimed invention*, and to refrain from creating a patchwork of passages from Hansen, based on hindsight, which do not support the rejection.

It will be seen upon reviewing the summary of claim 1 above that there are a large number of elements and steps which the references totally fail to teach.

Hansen

Contrary to the Examiner's interpretation of this reference as being relevant to the claimed invention, the process described in Hansen is unlike anything in the claimed invention. The Examiner is requested to reconsider the relevance of Hansen, especially taking into account the discussion below.

Hansen utilizes the process of *agglutination of beads* to create complexes of 2, 3, or more *clumps* and distinguishes them by their scatter properties. This is actually a good example illustrating the difficulty encountered in the early stages of bead based assays, namely, that investigators had real problems with bead clumping and had to live with it as an analytical tool. The presently claimed invention has virtually *eliminated the clumping issue* and uses pure scatter properties to distinguish the bead populations. Applicant is able to discretely separate individual, single bead sizes because of the unique properties of the coating and analysis procedures as set forth in the claims.

As quoted in Hansen, "the present invention relates to optical analytical methods based on rates of particle agglutination" (see column 1, lines 10 to 12). Hansen uses (Ab)-antigen A present in solution, which will couple beads containing antibodies to antigen A forming a bead complex. Likewise, the same is true for the detection of antibodies in samples to antigens.

Hansen fails to define the buffer, the protein, the specific bead-buffer matrix, adding the antigen to form the bead-antigen mixture, and then adding the buffer and reagent to incubate and reduce non-specific binding sites respectively. There are many procedures well known which use beads, washing, incubation etc.

It is also pointed out that the coefficient of variation of bead size, and the reducing of surfactancy, are two different events in the method. The Examiner seems to suggest in the office action that these are the same by stating that Hansen "teaches selecting the size of beads around coefficient of variation ... to reduce surfactancy of the beads". The bead size variation and the surfactancy levels are separate and discrete elements in the claims and each should be accorded its own weight in defining the method of the invention.

Bignami

Bignami teaches specific protein binding assays. As a general comment, this patent has nothing to do with the claimed invention. It is noted that the Examiner cites this patent to support the surfactancy characteristics of the method of the claimed invention. It is submitted that Bignami does not even remotely do this. Bignami merely makes brief reference to the "addition of surfactant" to lower the amount of non-specific binding or signal to noise ratio. There is absolutely no disclosure in Bignami

relating to the control of surfactancy of beads. There is nothing in this document which suggests or leads a person skilled in the art to control the surfactancy of beads, including when read with Hansen, and the Examiner is applying this patent with the hindsight of knowledge of the Applicant's claimed invention.

Fulwyler

The Examiner cites this document in rejecting claims 2, 3 and 4. A brief review of this reference will therefore be offered.

Applicant has developed a manner of coating the beads which is unique compared to the procedures in Fulwyler. Some of these difference are:

(1) Applicant does not use PBS at pH 7.0 or Tris Buffer pH 8.4. Even though buffer in appendix states making carbonate buffer pH 9.5, ours is bicarbonate and carbonate specialized mixtures.

(2) Applicant does not need PBS-BSA-Tween to wash the beads. This generally is used to prevent clumping. We have beads *formulated prior to coating that eliminates this problem* (see surfactancy component).

(3) Applicant requires only a protein/bead incubation in the refrigerator for 12 - 18 hours. No pre-incubation as in Fulwyler at 37 degrees for 3 hours is required.

(4) No 37 degree incubation for 1 hour for blocking is required. Applicant's invention is a one wash step with a low percentage of BSA in carbonate buffer.

(5) Storage - Applicant does not need to store beads in solutions containing glycerol. Applicant does not need to pre-wash the beads prior to usage.

(6) Applicant's invention is a "no-wash" assay (i.e. no washes between incubation steps), which is not the case with Fulwyler.

General Comments

The Examiner continues to review the claimed invention as a general type of disclosure when it recites specific steps and combinations not found or suggested in the prior art. For example, Applicant combines the variation of bead size and bead surfactancy to define a bead for use in the method which is simply not shown in the references cited.

The ability to prevent the beads from clumping (i.e. forming complexes of 2 or more beads) is significant, but the Examiner has not acknowledged that the claimed invention recites a method which addresses this issue and that the references cited simply are not able to achieve it. Applicant's invention accomplishes a way to virtually eliminate clumping phenomenon, unlike Hansen's patent whose entire premise is based on *agglutination*, the very *antithesis* of the method claimed in the present invention.

Further, Hansen utilizes light scatter properties to detect the aggregates of the beads. This only implements two of the possible analysis channels found in modern flow cytometers. He also uses a "Delta" difference in the refractive index between reactions occurring in the bead signals to determine differences, or variations, of the singlets versus the doublets and triplets or multiplexes of beads. This "Delta" is the measure of positivity. The claimed invention uses size discrimination for separating each bead and then fluorescent markers to detect the presence or absence of the specific binding of the antigen or antibody to the bound antigen or antibody, respectively. Hansen has limitations on the number of assays performed in one tube because of the interference agglutination may cause using multiple sized beads. The present invention uses discrete sizes which are easily recognizable and, therefore, have the ability to separately be distinguished one bead

assay from the other. This greatly facilitates user operation and interpretation.

In evaluating the claimed invention, the Examiner is requested to give due consideration to the steps of the invention as set out in the claimed invention and not to apply general principles of the art cited. The references should precisely support the rejections, and it is submitted that they do not.

In *In re Dembiczak* 175 F.3d 994, 50 USPQ2d 1614, (Fed. Cir. 1999), a Federal Circuit panel emphasized that, to reject an inventor's claim for obviousness in view of a combination of prior art references, a showing of a suggestion, teaching, or motivation must be "clear and particular." The Court stated:

> "We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, ... although 'the suggestion more often comes from the teachings of the pertinent references'. ... The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' (Emphasis added.) ... Nowhere does the Board particularly identify any suggestion, teaching, or motivation to combine ....(Emphasis added.)

Dembiczak made other important findings relevant to the present examination and some of these are set out below:

> "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but

critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."

"Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."

"Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight."

Applicant has already set out above the essential contents of claim 1 in this application. With the benefit of hindsight of the type mentioned in *Dembiczak*, the Examiner combines references despite the fact that none of them in any way suggests, teaches or motivates to make the combination of the Applicant.

Without doubt, there is nothing "clear and particular" (the *Dembiczak* standard) in these references to support the Examiner's findings. The Examiner has simply set forth broad conclusory statements regarding the teachings of these multiple references, which, standing alone, are *not evidence* of the type required to support an obviousness rejection. Nowhere does the Examiner particularly identify any suggestion, teaching, or motivation in these references to combine. This is because a detailed study of these references highlights the fact that *there is no* such suggestion etc.

If the Examiner has any questions, he is invited to contact the undersigned at (818)710-2788.

Please acknowledge receipt hereof by stamping and returning the enclosed return postcard.

Respectfully submitted,

Colin P. Abrahams (Reg. No. 32,393)
Attorney fo the Applicant
5850 Canoga Avenue, Suite 400
Woodland Hills, California 91367
Tel: (818)710-2788; Fax: (818)710-2798

Enclosed: Petition for extension, Check, Return postcard

Certificate of Mailing (37 CFR 1.8):
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on January 22, 2004.

Colin P. Abrahams

1007-103.US50